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(57) Abstract

Hydrophilic 2-phenylethylacrylate and 2-phenylethymethacrylate copolymer-based materials for use in the manufacture of introcular lenses with minimized risk for glistening.

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Foldable Intraocular Lens Materials.

The present invention relates to the field of intraocular lenses and to improved materials based on acrylate polymers, especially copolymers of 2-phenylethylacrylate and 2-phenylethylmethacrylate, to be used in the production of foldable lenses facilitating small incision surgery.

When an ophthalmic surgeon operates on an eye to remove a cataract (s)he frequently replaces the defective natural lens with a small artificial lens, an intraocular lens (IOL). The material most commonly used for the manufacture of IOLs has for many years been rigid amorphous plastic poly(methylmethacrylate) (PMMA).

In cataract surgery an incision must be made in the eye in order to remove the natural lens as well as for introducing the IOL. The minimum size of incision necessary to allow the passage of a rigid lens is about the diameter of the IOL (5.0-6.0mm) and in the development of such lenses considerable efforts have been focused on the design of the haptics to avoid incisions greater than the cross-section of the optical part of the lens. However, with these comparatively large incisions sutures are needed and the technique may give rise to various wound-related problems including infection, wound leak, and astigmatism.

For some years there have been on the market elastomeric silicone lenses of a design that allows the IOL to be reversibly deformed, for instance folded or rolled-up, prior to insertion, so that the size of the incision

required is about halved to around 3.0mm. This was preceded by the development of the phacoemulsification technique for extra capsular cataract extraction which means that the natural lens can be removed through a small incision. The introduction of the smaller wound technique, which eliminates the need for sutures, allows less restricted early postoperative physical activity and more rapid optical rehabilitation.

Whilst the advantages of elastomeric silicone IOLs is well established, these lenses have some limitations, in particular most silicones have a lower refractive index than PMMA (1.49). A consequence of the lower refractive index of silicone elastomers is the requirement for a thicker lens for any given dioptre than is necessary for PMMA. This factor taken together with the high rubber elasticity of silicone lens material, results in the rapid and powerful recovery of the folded IOL, which is undesirable in the context of a posterior chamber lens.

To overcome some of these disadvantages alternative flexible lens materials have been sought which combine a high refractive index with a lower elasticity. Acrylic polymers have been favoured by some manufacturer of lenses because of their biocompatibility, ease of preparation, high level of atacticity - ensuring low crystallinity and hence high optical clarity, good processing characteristics, and long term stability to UV.

A typical method of producing such acrylic polymers is by copolymerisation. Thus in EP 91310271.1 and US 5290892, to Nestle SA, is reported the preparation of copolymers of 2-phenylethylacrylate,

2-PEA, and 2-phenylethylmethacrylate, 2-PEMA, for use in the manufacture of IOLs. These copolymers have refractive indices close to 1.55, glass transition temperatures (Tg) below 37°C, and an elongation of 200%, and so, in IOL-form, may be folded, and have a reduced thickness for any dioptre when compared with silicone lenses which in most cases have lower refractive indices.

Recently it has become apparent that IOLs made from copolymers of 2-PEA and 2-PEMA, exemplified by Acrysof from Alcon, suffer from glistening during their clinical use. This internal opacification arises from vacuoles of upto 2 μm in length. Vacuoles are formed by the absorption, by a lens, of water from the aqueous humor, surrounding the lens in the eye. The reason for this is most likely that in a hydrophobic polymer like Acrysof absorbed water may phase-separate forming microvacuoles. Such microvacuoles are, or may serve as, the initiation sites for the microcracks, and it is assumed that this causes glistening in Acrosof type materials.

Scope of the Invention:

We have found that already a small increase in the hydrophilicity of the 2-PEA/2-PEMA copolymer-based materials will prevent the internal opacification of lenses made from them. This finding is of course valid even if the mechanism discussed above would be found incomplete or even less correct. The hydrophilicity of these copolymers is improved by introducing, in low molar ratio, in the range 0.1 to 10 mole%, a third monomer of recognised hydrophilic character, e.g. monomers such as acrylic acid, methacrylic acid, hydroxyethylacrylate, hydroxyethylmethacrylate, acrylamide, methacrylamide, poly(ethylene

glycol) acrylates (PEG-acrylates) and other similar monomers (preferably unsaturated compounds), especially those containing carboxyl-, hydroxyl- sulphate- or sulphonate-, amido- or substituted amino-bearing groups, known to those skilled in the art of polymer chemistry.

The 2-PEA/2-PEMA copolymer-based materials to be used according to the present invention in the manufacture of IOLs are characterized in that they are made hydrophilic enough to prevent the formation of microvacuoles with subsequent glistening of the material. Accordingly, the materials are characterized in that no internal two-phase system is formed in contact with an aqueous solution. The materials have a degree of swelling in the range of from 0,5-10, for instance 1-5, wt% at saturation, i.e. following immersion in isotonic solution at 37 °C for 24 hours.

For the preparation of polymers of improved hydrophilicity for the manufacture of foldable IOLs, mixtures of 2-PEA and 2-PEMA, in the range of molar ratios as described in US 5290892, hereby incorporated by reference, are combined with one or more hydrophilic monomers, e.g. from the group of compounds referred to above. The mixture of three or more monomers may be converted into a tercopolymer, etc., by conventional free radical polymerisation, in bulk, aqueous suspension or emulsion, or in solution in a suitable solvent, such as toluene.

An alternative approach to the introduction of the hydrophilic acid monomer, such as acrylic and methacrylic acids into the 2-PEA/2-PEMA copolymer system may also be adopted. This method involves the

synthesis of an acrylic acid/methacrylic acid copolymer, followed by its conversion to desired copolyester. In such copolymers, the acrylate monomer constitutes from 60mole% to 99mole% of the polymer, while the methacrylate monomer constitutes from 40mole% to about 1mole%. Preferred are polymers consisting of 90-95mole% acrylic acid, AA, and 10-5mole% methacrylic acid, MAA. Such copolyacids may be prepared in aqueous or benzene (or other aromatic solvent) solution by the free radical polymerisation of the component monomers (AA and MAA).

Such polyacids may then be, partially, converted to the desired copoly(acrylate-methacrylate ester), which contains residual free carboxyl groups. Many different methods of producing polyesters from polyacids are reported in the literature, for example the poly(acid chloride) or a poly(acid anhydride) may be reacted with an excess of the alcohol of the alkyl, aryl or alkylaryl group it is intended to substitute for the acid proton. Thus a copolymer of AA and MAA is converted to a copolymer of acryloyl chloride and methacryloyl chloride by reaction with phosphorus pentachloride, phosphoryl chloride or thionyl chloride and a copolymer of 2-PEA and 2-PEMA synthesised from it by reaction with excess of 2-phenylethyl alcohol.

In an alternative reaction the AA/MAA copolymer is converted to a copolymer of mixed acid anhydrides by reacting with acetic anhydride. This mixed anhydride copolymer may then be used to produce the desired copolymer of 2-PEA and 2-PEMA, by reacting it with 2-phenylethyl alcohol. Other methods of preparing esters from carboxylic acids well known to those skilled in the art of organic synthesis may also

be adapted for the preparation of copolymers 2-PEA and 2-PEMA, for example, methods involving phase transfer catalysts.

However, most of these methods do not readily lend themselves to the controlled conversion of AA/MAA copolymers such that a selected molar fraction of carboxylic groups is retained in the 2-PEA and 2-PEMA copolymer, which results. A preferred method of synthesis in this context is the following approach.

The dry AA/MMA copolymer is dissolved in dimethylsulphoxide and reacted with 2-phenylethyl bromide, in the presence of a catalyst, such as 1,8-diazabicyclo[5,4,0]-7-undecene. The reaction time and temperature are controlled so that substitution of the acid groups by 2-phenylethyl groups is in the range 80-99.9mole%, with the residual carboxyl bearing monomer group, the hydrophilic group, present in the range 200-0.1mole%.

An additional alternative method of producing 2-PEA/2-PEMA copolymers of improved hydrophilicity is by their chemical modification. Using 2-PEA/2-PEMA copolymers having a composition in the range as specified in US 5290892 as suitable for the manufacture of IOLs, acid groups are introduced by their partial de-esterification by electron beam irradiation, or by treatment with acid or base. Such treatments may be applied to the material in the bulk condition to introduce acrylic and methacrylic acid groups. They are also effective for the surface modification of IOLs produced from 2-PEA/2-PEMA copolymers, allowing for the fixation, covalent coupling of surface treatments, for instance mucopolysaccharides, e.g. hyaluronic acid,

chondroitin sulphate or heparin, to improve biocompatibility of the IOL, and/or to impede the development of a secondary cataract.

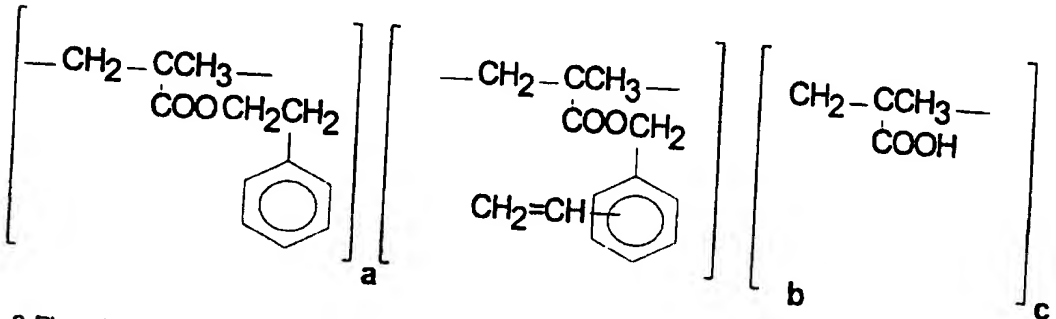
One method of doing this, involving reacting the surface carboxyls with a polyamine, e.g. poly(ethyleneimine) and attachment of the mucopolysaccharide, e.g. heparin via a Schiff's base reaction, followed by reduction (se for instance EP 86186). Alternative methods of attachment are also possible including using a poly(ethylene oxide) spacer, or the use of an albumin-heparin conjugate.

Yet another method to produce the desired copolymer (which will be in this case a graft copolymer) is to use a 2-phenylethylmethacrylate /styrylmethylmethacrylate/methacrylic acid tercopolymer, such as (I), as the cross-linking agent for a 2-phenylethylacrylate/(meth)acrylic acid elastomer.

The composition of (I), the cross-linking agent, is (a) 2-phenylethylmethacrylate, 80 to 99.9 mole %; (b) a (meth)acrylate bearing a free vinyl group, e.g., a styryl group as shown in (I), or a 2-hydroxy-3-(meth)acrylpropyl group, or allyl group, etc., 0.1 to 20 mole %; and a hydrophilic monomer, such as (meth)acrylic acid, (meth)acrylamide, N,N-dimethyl(meth)acrylamide, or 2-hydroxyethyl(meth)acrylate, 0 to 2 mole %.

To produce a sheet material for IOL production, 0.1 to 10 weight % of the tercopolymer of type (I), is dissolved in a mixture (99.9 to 90 weight % of combined monomers) of 2-phenylethyl-acrylate (99.9 to 90 mole

%) and a second (meth)acrylate monomer of a hydrophilic nature, such as (meth)acrylic acid, (meth)acrylamide, N,N-dimethyl(meth)acrylamide, or 2-hydroxyethyl(meth)acrylate (0.1 to 10 mole %), together with a free radical initiator, such as benzoyl peroxide, or azobisdiisobutyronitrile (0.025 to 5 weight %).



2-Phenylethylmethacrylate/styrylmethylmethacrylate/methacrylic acid tercopolymer (I)

Such formulations may be converted to cast sheets of cross-linked copoly(2-phenylethyl-acrylate) elastomers by the conventional 2-step procedure. For this process the first step is to prepare a casting syrup by heating the mixture of monomers, cross-linking agent and thermal free radical initiator, at temperatures near to 80°C for 5 to 30 minutes. Then the second step is to transfer the resulting thick polymerising syrup to a cell suitable for casting sheets, and advance the polymerisation to completion by subjecting the cell to an appropriate heating regime, e.g., 2 to 10 hours at 40 to 80°C followed by 2 to 10 hours at 80 to 140°C. IOLs may be lathe-cut from the resulting sheets, preferably whilst holding the temperature of the sheets below 0°C, that is below their T_gs.

Claims:

1. 2-phenylethylacrylate and 2-phenylethylmethacrylate copolymer-based material for use in the manufacture of intraocular lenses characterized in that the material is hydrophilic.

2. Materials according to claim 1, characterized by 0.5-10, preferrably 0.5-5, % water uptake at saturation.

3. Materials according to any one of claims 1-2 characterized in that a third monomer, containing carboxyl-, hydroxyl-, sulphate, sulphonate, poly(ethylene glycol), amido- or substituted amido- bearing groups, is introduced into the reaction mixture prior to polymerisation.

4. Material according to claim 3 characterized in that it contains carboxyl groups.

5. Material according to claim 1, characterized in that the surface is modified to contain a layer comprising a mucopolysaccharide.

6. Material according to claim 5, characterized in that the muchopolysaccharide is heparin.

7. Intraocular lens prepared from a material according to any one of claims 1-6.

8. Intraocular lens according to claim 7 which further comprises a surface bound substance preventing secondary cataract.

INTERNATIONAL SEARCH REPORT

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PCT/SE 96/01722

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C08F 220/30, G02B 1/04
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C08F, G02B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 9611235 A1 (PHARMACIA AB), 18 April 1996 (18.04.96), page 4, line 3 - line 18, abstract	1-8
A	WO 9511279 A1 (ALCON LABORATORIES, INC.), 27 April 1995 (27.04.95), page 13, line 14 - line 15	1-8
A	WO 9411764 A2 (ALLERGAN, INC.), 26 May 1994 (26.05.94), page 8, line 34 - page 9, line 22, abstract	1-8

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

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International application No.
PCT/SE 96/01722

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0485197 A1 (NESTLE SA), 13 May 1992 (13.05.92), page 3, line 21 - line 56, claims 8-10, abstract --	1-8
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INTERNATIONAL SEARCH REPORT

Information on patent family members

04/03/97

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